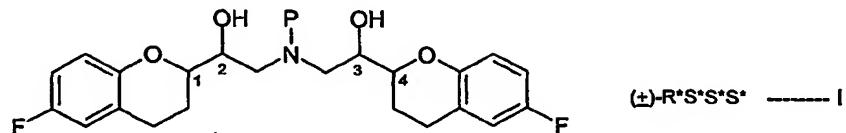
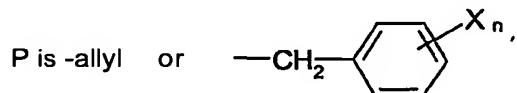


We claim:

1. A process for preparing acid additional salts of compounds of formula I:



5 wherein

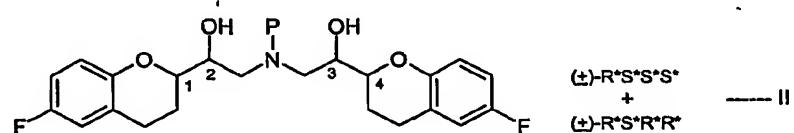


wherein

X each independently is halo, nitro or C₁-C₃ alkyl and n is 0 - 5;

which comprises:

10 1a) treating a mixture containing racemic diastereomers of a compound of formula II:



wherein P is as defined in formula I;

with a suitable acid to form the corresponding acid addition salt;

15 1b) subjecting the acid addition salt obtained in step (a) to the fractional crystallization from an alcoholic solvent, ketonic solvent, acetonitrile, dimethylformamide, dimethylsulfoxide and tetrahydrofuran or mixture thereof to obtain the diastereomeric pair of compound of formula I.

2. The process according to claim 1, wherein the alcoholic solvent is selected from the group consisting of C₁ to C₅-alcohols.

3. The process according to claim 2, wherein the alcoholic solvent is selected from methanol, ethanol, propanol and isopropyl alcohol.

4. The process according to claim 3, wherein the alcoholic solvent is ethanol.

5. The process according to claim 1, wherein the ketonic solvent is selected from the group consisting of C₃ to C₈-ketones.

6. The process according to claim 5, wherein the ketonic solvent is selected from acetone, methyl isobutyl ketone and methyl tert-butyl ketone.
7. The process according to claim 6, wherein the ketonic solvent is acetone.
8. The process according to claim 1, wherein the acid addition salt is prepared by treating the mixture containing compounds of formula II with the corresponding acid in a solvent.
- 5 9. The process according to claim 8, wherein the acid is inorganic acid or an organic acid.
- 10 10. The process according to claim 9, wherein the inorganic acid is a hydrogen halide, nitric acid or phosphoric acid.
11. The process according to claim 10, wherein the hydrogen halide is hydrogen chloride.
12. The process according to claim 9, wherein the organic acid is a carboxylic acid or a sulfonic acid.
- 15 13. The process according to claim 12, wherein the carboxylic acid is selected from acetic acid, propanoic acid, formic acid, hydroxyacetic acid, 2-hydroxy propanoic acid, 2-oxopropanoic acid, propane dioic acid, butanedioic acid, (Z)-2-butenedioic acid, (E)-2-butenedioic acid and 2-hydroxy butanedioic acid.
- 20 14. The process according to claim 12, wherein the sulfonic acid is selected from methane sulfonic acid, toluene sulfonic acid and benzene sulfonic acid.
15. The process according to claim 8, wherein the solvent is an organic solvent.
16. The process according to claim 15, wherein the organic solvent is selected from the group consisting of C₁ to C₅-alcohols, C₃ to C₈-ketones, C₂ to C₈-esters, acetonitrile, tetrahydrofuran, dimethylformamide, dimethylsulfoxide, 25 dioxane, aromatic hydrocarbons, C₁ to C₅-halogenated hydrocarbons and C₂ to C₈-ethers and mixture thereof.
17. The process according to claim 16, wherein the alcoholic solvents are methanol, ethanol, propanol and isopropyl alcohol; ketonic solvents are acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone and diethyl ketone; ester solvents are ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate; aromatic hydrocarbon solvents are benzene, toluene and xylene; halogenated hydrocarbon solvents are methylene chloride, chloroform,
- 30

carbontetrachloride and ethylene dichloride; and ether solvents are tert-butyl methyl ether and diethyl ether.

18. The process according to claim 16, wherein the organic solvent is selected from methanol, ethanol, propanol, isopropyl alcohol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone, diethyl ketone, acetonitrile, dimethylformamide, dimethylsulfoxide and tetrahydrofuran.

5 19. The process according to claim 18, wherein the organic solvent is methanol, ethanol or acetone.

10 20. The process according to claim 1, wherein the fractional crystallization is carried out in anhydrous condition.

21. The process according to claims 1 and 20, wherein the crystallization is carried out by cooling, addition of anti-solvents, seeding or partial removal of the solvents or combination thereof.

15 22. The process according to claim 21, wherein the crystallization is carried out at about 0°C to 45°C.

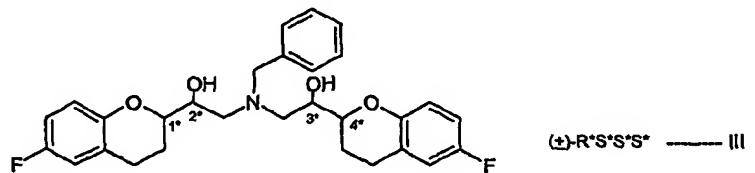
23. The process according to claim 22, wherein the crystallization is carried out at about 0°C to 35°C.

24. The process according to claim 1, wherein the steps (a) and (b) are performed in the same solvent or different solvent.

20 25. The process according to claim 24, wherein the steps (a) and (b) are performed in different solvents.

26. The process according to claim 1, wherein the acid addition salts of formula I are prepared from the reaction mass obtained as a part of the synthesis of the compounds of formula II.

25 27. The process according to claims 1 and 26, wherein the acid addition salts of compound of formula I prepared according to the present invention are hydrogen halide addition salts of formula III:



28. The process according to claim 27, wherein the hydrogen halide salt of formula III is hydrogen chloride salt.

29. A process for the preparation of nebivolol or a pharmaceutically acceptable salt thereof, which comprises the steps of:

5 a) reacting 6-fluoro-3,4-dihydro- α -[(phenylmethyl)amino]methyl]-2H-1-benzopyran-2-methanol with 6-fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran in an C_1 to C_5 -alcohol or C_3 to C_8 -ketone solvent to produce (+)-[2R*[1S*,5S*(S*)]]+[2R*[1S*,5R*(R*)]]- α,α' -[phenylmethylinobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol];

10 b) treating (+)-[2R*[1S*,5S*(S*)]]+[2R*[1S*,5R*(R*)]]- α,α' -[phenylmethylinobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] produced in step (a) with hydrogen halide, sulfate or hydrogen sulfate; subjecting to fractional crystallization at about 0°C to 45°C and filtering the separated solid to produce corresponding salt of (+)-[2R*[1S*,5S*(S*)]]- α,α' -[phenylmethylinobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol];

15 c) basifying the salt of (+)-[2R*[1S*,5S*(S*)]]- α,α' -[phenylmethylinobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] produced in step(b) in a solvent to produce (+)-[2R*[1S*,5S*(S*)]]- α,α' -[phenylmethylinobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] free base; and

20 d) subjecting (+)-[2R*[1S*,5S*(S*)]]- α,α' -[phenylmethylinobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] free base to catalytic hydrogenation with hydrogen using palladium on carbon as catalyst to obtain nebivolol optionally converting to the pharmaceutically acceptable salt.

25 30. The process according to claim 29, wherein the alcoholic solvent is selected from the group consisting of C_1 to C_5 -alcohols.

31. The process according to claim 30, wherein the alcoholic solvent is selected from methanol, ethanol, propanol and isopropyl alcohol.

30 32. The process according to claim 31, wherein the alcoholic solvent is ethanol.

33. The process according to claim 29, wherein the ketonic solvent is selected from the group consisting of C_3 to C_8 -ketones.

34. The process according to claim 33, wherein the ketonic solvent is selected from acetone, methyl isobutyl ketone and methyl tert-butyl ketone.

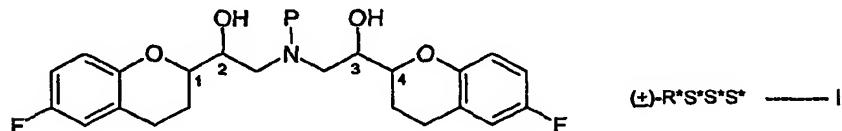
35. The process according to claim 34, wherein the ketonic solvent is acetone.

36. The process according to claim 29, wherein the hydrogen halide is hydrogen chloride.

37. The process according to claim 36, wherein the treatment in step (b) is carried out by passing hydrogen chloride gas to the mass containing $(+)$ - $[2R^*[1S^*,5S^*(S^*)]] + [2R^*[1S^*,5R^*(R^*)]] - \alpha,\alpha'$ -[phenylmethyliminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]

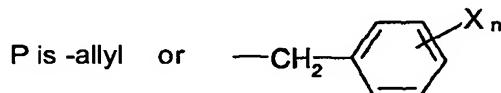
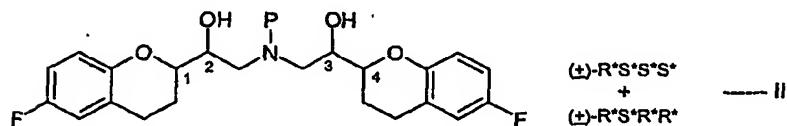
10 (or) by adding a solution of hydrogen chloride in a solvent to the mass containing $(+)$ - $[2R^*[1S^*,5S^*(S^*)]] + [2R^*[1S^*,5R^*(R^*)]] - \alpha,\alpha'$ -[phenylmethyliminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol].

38. Acid addition salts of formulas I and II:



15

wherein

wherein X each independently is halo, nitro or C₁-C₃ alkyl and n is 0 - 5;

20

wherein P is as defined in formula I.

39. The acid addition salts of claim 38, wherein the said salts are hydrogen halides, hydrogen sulfates, sulfates and sulfonic acid salts.

40. The acid addition salts of claim 39, wherein the said salts are hydrogen halides.

25

41. The acid addition salts of claim 40, wherein the said salts are hydrogen chloride, hydrogen iodide and hydrogen bromide.

42. The acid addition salts of claim 41, wherein the said salt is hydrogen chloride.

5

10

15